Wednesday, July 12, 2002

CTEP Amendment-request Submission Policy And Frequently Asked Questions

What is an Amendment-Request?

All changes made to a protocol MUST be approved by CTEP prior to implementation (see exception for Editorial or Administrative Updates). Changes to a protocol shall be submitted to CTEP in the form of an Amendment-request. The policies regarding Amendment-requests are described below.

Who can submit an Amendment-Request Submission?

To maintain consistency of the protocol document CTEP will only accept Amendment-request submissions from the Principal Investigator or Protocol Chair (for Group studies) of a study. Co-investigators cannot submit protocol amendments. Amendment-requests submitted by anyone other than the Principal Investigator or Protocol Chair will be denied and returned to the submitter. Local policy (your organization) may require that all Amendment-requests be processed through a central operations office.

All Amendment-requests for NCI Cooperative Group studies MUST be routed through the Group operations office. CTEP will NOT accept an Amendment-request that has not been routed through the appropriate local channels (i.e. Group or Cancer Center operations office). An Amendment-request that has not gone through the proper channels will be denied and forwarded to your local (i.e. Group) operations office.

Complete Amendment-Request Submissions:

The following documentation MUST be included with every Amendment-request submission:

- Cover letter – The cover letter shall identify by page AND section each change made to a protocol document. All changes shall be described in a point-by-point format (i.e. Page 3, section 1.2, replace 'xyz' and insert 'abc'). When appropriate a brief justification for the change should be included.
- A revised un-marked (without handwritten notes or highlights) copy of the protocol document that accurately reflects the Amendment-request submission cover letter. INCLUDING:
    - All protocol attachments listed in the table of contents regardless of whether any changes occurred to these sections.
    - The entire Informed Consent regardless of whether any changes occurred to this document.
- Ancillary supporting documentation as required (i.e. IRB approval for addition of a new institution to a non-Group study)

- The protocol title page shall include a Version and Update-date that reflects the time-point of the most recent change to the document (see Version-date vs Update-date policy below).
- If the amendment is in response to a CTEP or FDA request for change the original change request letter shall be attached.
- If local (i.e. your organization) policy requires inclusion of version dating of each individual change throughout the protocol document, then the date-changed for each line-item MUST be included in the Amendment-request cover letter. Example:
    - Page 5, Section 2.1: Has been changed from "PK samples will be sent to 123 Main st., Anytown USA" to "PK samples will be sent to 456 Broadway, Anytown, USA". This change was made effective ##/##/####.
- OPTIONAL – In addition to the above, you may include a revised copy of the protocol with all changes specified in the Amendment-request cover letter highlighted throughout the document utilizing a word-processing program.

Amendment requests that do NOT include ALL the above documentation will be placed on-hold and the site contacted to submit the missing information. The Amendment-request will NOT be processed and reviewed by CTEP until all required documentation is submitted. Attached below is an Amendment-request Submission Checklist that can be utilized by your staff to verify that the Amendment-request is complete. NOTE: CTEP does NOT require that the Amendment-request Submission Checklist be included with your submission.

Protocol and Information Office
Cancer Therapy Evaluation Program, DCTD, NCI
Executive Plaza North, Rm. 7000
Rockville, MD 20892
pio@ctep.nci.nih.gov

Amendment-Request Submission Checklist

NCI Protocol #: Organization (local) Protocol #

DID YOU INCLUDE THE FOLLOWING?

Check

- ☐ A detailed cover letter that clearly identifies, by page AND section each change made to a protocol document. All changes will be listed and described in a point-by-point format (i.e. Page 3, section 1.2, replace 'xyz' and insert 'abc'). When appropriate a brief justification for the change should be included.

- ☐ A revised un-marked (without handwritten notes or highlights) copy of the protocol document that accurately reflects the Amendment-request submission cover letter. INCLUDING:
  - All protocol attachments listed in the table of contents regardless of whether any changes occurred to these sections.
  - The Informed Consent regardless of whether any changes occurred to this document.

- ☐ The protocol title page shall include a Version date and an Update-date that reflects the time-point of the most recent changes to the document (see Amendment FAQs).

- ☐ If the amendment is in response to a CTEP or FDA request for change the original change request letter shall be attached.

- ☐ OPTIONAL – In addition to the above the site may include a revised copy of the protocol with all changes specified in the Amendment-request cover letter highlighted throughout the document.

Amendment-requests that do NOT include ALL the above documentation will be placed on-hold and the site contacted to submit the missing information. The amendment request will NOT be processed and reviewed by CTEP until all required documentation is submitted.

Draft Amendments

CTEP will NOT accept a draft of a proposed amendment. There shall be no indication anywhere in the protocol document that it is a draft (document stamped 'draft'). Documents stamped 'draft' will be returned to the investigator without CTEP review.

Editorial or Administrative Updates

What is an Editorial or Administrative Update?

Editorial or Administrative Updates are those changes to a protocol document that do NOT affect the scientific intent of the study or human subject protection. Editorial or Administrative Updates can be made without prior CTEP review and approval. Investigators should follow local IRB policy and procedures regarding Editorial or Administrative Updates. The protocol title page should reflect the latest Update-date as well as the Protocol Version-date (See Version-date vs. Update-date section).

Any change that affects the scientific intent, study design or human subject protection is considered an amendment and therefore MUST be approved by CTEP and your IRB prior to implementation.

Examples of changes that CTEP considers Editorial or Administrative Updates are:

- Typographical correction, except if patient safety is involved (i.e. change eligibility from < to > XYZ; or change dose from mg to mcg).
- Re-phrasing a sentence or section to add clarity as long as the change does NOT affect the scientific intent, study design or human subject protection.
- Re-formatting the document as long as the change does NOT affect the scientific intent, study design or human subject protection.
- Address, telephone, E-mail changes, except changes to the Principal Investigator or Protocol Chair contact information. Note: CTEP should be notified through the FDA form 1572 process of any change in address for any investigator (principal or co-investigator) identified on the title page of a study that utilizes a PMB supplied agent.
- Addition/deletion of physician co-investigators to studies that do NOT utilize a PMB supplied agent.
- Addition/deletion of non-physician co-investigators to any trial.
- Addition/deletion of an institution to a CTEP U10 Cooperative Group 'Group-wide' study.

Protocol changes that do NOT meet the above examples above should be considered amendments and therefore MUST be submitted and approved by CTEP in the form of an Amendment-request prior to implementation. To add further clarity the following protocol changes are considered amendments and therefore require prior CTEP approval:

- Typographical correction that may affect patient safety (i.e. change eligibility from < to > XYZ; or change dose from mg to mcg).
- Addition/deletion of an institution to a CTEP U10 Cooperative Group 'limited-

institution' study if the participants are individually named on the title page of the study.

- Addition/deletion of physician co-investigators to studies that utilize a PMB supplied agent.
- Re-phrasing a line or section that results in a change of scientific intent, study design or affects human subject protection.
- Re-formatting the document that results in a change of scientific intent, study design or affects human subject protection.
- A change of Protocol Chair or Principal Investigator.
- A change in protocol status. Status changes may also be sent via the CDUS.
- A change of institution for the principal investigator or any physician co-investigator on a study with a PMB supplied agent.
- Addition/deletion of a Group to an InterGroup study.
- A change in accrual targets

How/when should CTEP be notified of Editorial or Administrative Updates?

CTEP may be informed of Editorial or Administrative Updates, in one of three ways. The first two methods are preferred since this will cut down on everyone's workload. CTEP should be informed, through the Amendment-request submission process of Editorial or Administrative Updates within at least one-year of the modification:

- Batch – All Editorial or Administrative Updates for a given study during the year can be assembled together and reported at one time.
- Combine with scientific, study design or human subject protection amendments – Editorial or Administrative Updates can be incorporated into an amendment that relates to scientific or human subject protection issues.
- PRN – As the changes occur an Editorial or Administrative Update can be submitted to CTEP.

Posting Amendments on the Internet

Only CTEP approved amendments may be posted on the Internet for general notification of their membership and participants. Prior to CTEP approval amendments may only be distributed in a limited manner to those individuals that are required to review and assess the requested changes. Exception: Editorial or Administrative Updates (described above) may be posted on the Internet without prior CTEP approval.

Status Updates

Status changes are not amendments per se. CTEP should be notified regarding any change in protocol status in a timely fashion. In general CTEP would recommend that status changes not be incorporated with other protocol changes (amendments). All communication to CTEP regarding status changes MUST use the CTEP terms and definitions for protocol statuses (listed below). All Clinical Data Update System (CDUS) submissions should be consistent with the latest protocol status notification. CTEP terms and definitions for protocol status:

CDUS Code	Status Term	Status Definition
AP	Approved	Trial is active but no patients have been accrued.
AC	Active	Trial is open and accruing.
TC	Temporarily Closed to accrual	Trial is temporarily not accruing.
TB	Temporarily Closed to accrual and treatment	Accrual has been temporarily suspended and patients are NOT receiving therapy.
CL	Closed, patients still on treatment	The protocol has been closed to patient accrual. Patients are still receiving therapy.
CB	Closed, all patients have completed treatment	The protocol has been closed to patient accrual. All patients have completed therapy, but patients are still being followed according to the primary objectives of the study. No additional investigational agents are needed for this study.
CP	Complete	Trial is closed to accrual and all patients have completed treatment. The study has met its primary objectives. This is the final study report.

Activation Amendments

The Principal Investigator or Protocol Chair shall notify CTEP when a study is ready to be activated. An active study is defined as a study that is open and accruing. CTEP approval is NOT required to activate the study. An activation amendment is a means to notify CTEP of the change in status. CTEP strongly discourages the incorporation of other changes in an activation amendment, but a site may still include them if they so choose.

If a site incorporates the 'Activation Notice' with other changes, the document will be treated as an Amendment-request submission. Therefore, the study CANNOT be activated or any changes implemented until CTEP has approved the amendment.

Version-date vs. Update-date

Version-date

The Version-date is the day that reflects the most recent amendment to a protocol document. CTEP and others (IRB, CIRB, CTSU, local institutions) will use the version date to identify the latest edition of a protocol document. The Version-date shall be clearly identified on the protocol title page and include month, day and year (i.e. Version: ##/##/####). CTEP would recommend that the Version-date correspond to the day the amendment was submitted to CTEP. Investigators may though use local policy to assign the Version-date (i.e. date PI or Study Chair approved amendment).

Update-date

The Update-date is the day that reflects the most recent Editorial or Administrative Update to a study (see the Editorial and Administrative Update policy). The Update-date shall be clearly identified on the protocol title page and include month, day and year (i.e. Update: ##/##/####). In most cases the Update-date should be equal to or greater then the Version-date.

Can other dates or a Version or Update number appear on the title page of the protocol?

CTEP recommends that the version number (a sequential number that identifies the latest amendment) be included on the title page of a protocol. Based on local (your organization) policy, other dates or milestones (i.e. CTEP approval, IRB approval, activation, etc.), MAY be included on the title page of the study. The Version-date and Update-date shall be clearly identified to distinguish it from any other dates on the title page of the study.

Are the Version and Update-dates affected by modification of a local milestone date (i.e. IRB approval date, protocol activation date)?

No, if local policy (your organization) requires inclusion of other dates (i.e. CTEP approval, IRB approval, activation, etc.), on the protocol title page, you should NOT modify the Version or Update-dates as these other milestone dates are changed. For example IF local policy requires recording of the IRB approval date on the protocol title page:

- Record the IRB approval date on the protocol title page of the study once IRB approval has been obtained.
- Do NOT modify the Version or Update-dates to reflect the recording of the IRB approval milestone.

All other changes should result in either a change to the Version or Update-dates or both.

Does CTEP require that all changes be tracked and dated individually within the body of the protocol document?

CTEP requires that the protocol title page reflect the most recent Version and Update-dates. CTEP does NOT require that all changes be dated individually within the body of the protocol document. If local (your organization) policy requires dating of individual changes within the body of the protocol:

- Note date of change in the body of the protocol.
- Modify the Version and/or Update-dates on the protocol title page.
- When an Amendment-request is submitted the date-changed for each line item MUST be included in an Amendment-request cover letter. For example:
    - Page 5, section 2.1: Has been changed from "PK samples will be sent to 123 Main St., Anytown USA" to "PK samples will be sent to 456 Broadway, Anytown, USA". This change was made effective ##/##/####.

Why Version Dating?

Substantial delays and confusion are frequently encountered as a result of the inconsistent approach to amendment numbering and dating. This confusion often results in delays in amendment reviews and approval. The problem stems from the inability of all parties to effectively track the 'active' version of an amendment or protocol. It is not uncommon for amendments to go through multiple iterative review cycles until approved. Without appropriate version control the amendment review process is often very cumbersome. A heightened awareness of this issue has resulted from the involvement of the CIRB and CTSU in the amendment review and approval process.

How to Send Amendment-requests

CTEP strongly recommends that all Amendment-request submissions be sent via e-mail to the Protocol and Information Office (PIO@ctep.nci.nih.gov). All appropriate documentation for the Amendment-request MUST be included in the e-mail (see the above policy for complete Amendment-request submission). The preferred format is Word®, but CTEP will accept most major file formats including WordPerfect®, PDF and ASCI.

Amendment-requests should NOT be sent via multiple different mechanisms (i.e. e-mail, express courier, US mail, etc.) as this will cause delays in processing times.

IND Safety Reports vs. IND AE Action Letters

CTEP informs investigators of Adverse Events (AE) observed with a CTEP IND agent via two different mechanisms, IND Safety Reports and IND AE Action Letters. The requirement for amending studies differs slightly between the two types of notifications.

IND Safety Reports

IND Safety Reports keep investigators apprised of those expedited adverse event reports that have been filed to the FDA by CTEP. Investigators are requested to file a copy of the report with their protocol and to send a copy to their IRB according to the local IRB's policies and procedures. CTEP does NOT require that the protocol or Informed Consent document be modified based on an IND Safety Report.

IND AE Action Letters

IND AE Action Letters are issued by CTEP for those serious adverse events that warrant a change in the Informed Consent document and/or protocol. The letter will specify if accrual to the protocol is to be suspended until the revision is made and whether patients previously enrolled on study require re-consenting. Investigators are provided a time frame for which to submit the amendment to CTEP's Protocol and Information Office.

Agent Comprehensive AE List vs. Agent Specific Expected Adverse Event List (ASAEL)

Agent Comprehensive AE List
The Comprehensive AE List represents a summary of ALL known AEs for an CTEP IND agent in both professional and laymen's terms (for informed consents).

Agent Specific Expected Adverse Event List (ASAEL)
The ASAEL identifies those AEs that are considered expected and do NOT require expedited reporting via AdEERS unless otherwise indicated (i.e. grade 4 or 5, or grade 3 precipitating hospitalization). AdEERS checks the ASAEL list to determine whether an AE is reportable based on the NCI AE Reporting Guidelines. The ASAEL represents a subset of the Agent Comprehensive AE List.

Which AE list should be inserted into the protocol?
The Agent Comprehensive AE List should be incorporated into the protocol document and the Informed Consent. CTEP would recommend that the ASAEL NOT be included in the protocol document. Investigators should refer to AdEERS to identify whether an AE requires expedited reporting. Exclusion of the ASAEL from the protocol document MAY minimize the need to amend the study.

CTEP or FDA Requests for Amendment

As the IND or trial sponsor CTEP MAY on occasion request that a study be modified. The FDA as a regulatory agency may also require that a study be modified. CTEP will notify the study Principal Investigator or Study Chair regarding the issues that require amendment. The letter will describe what changes are required, when the Amendment-request submission is required and any other details (i.e. temporary study closure, IRB notification, etc.). An Amendment-request in response to a CTEP or FDA request should NOT incorporate other protocol changes. The CTEP or FDA request shall be included by the Principal Investigator or Study Chair as part of the Amendment-request submission packet.

Emergency approval of an Amendment Request

An investigator may contact CTEP by telephone to obtain emergency approval of a change in those rare circumstances where an immediate change is necessary to assure patient safety. The point of contact will typically be the CTEP Investigational Drug Branch physician responsible for the investigational agent utilized on the study. A written Amendment-request must be submitted within 3 working-days.

Central IRB (CIRB) Review Process

Most amendments for CTEP sponsored phase 3 trials are reviewed by the NCI Central IRB (CIRB). The CIRB review process is separate and distinct from the CTEP review process. Amendments for CTEP sponsored phase 3 trials though require BOTH CTEP

and CIRB approval prior to implementation. The CTEP/CIRB reviews occur in a sequential fashion.

Any amendment considered 'approvable' by CTEP is forwarded to the CIRB for review. CTEP will send the investigator notification that the study has been 'approved on-hold' pending CIRB review. The amendment can NOT be implemented until the Principal Investigator or Study Chair receives an 'Approval-letter' from CTEP.

The CIRB will directly contact the study Principal Investigator or Chair to resolve any CIRB questions. All communication at this stage is between the CIRB and the study Principal Investigator or Chair. The study Principal Investigator or Chair shall ONLY address the CIRB comments and questions. Additional 'investigator-initiated' changes should NOT be directed to the CIRB without prior review and approval by CTEP. Investigator initiated changes MUST be submitted to CTEP directly. These changes will be treated as a separate amendment.

Once the CIRB is satisfied with the study the CIRB will notify both CTEP and the study Principal Investigator or Chair. NOTE: The amendment can NOT be implemented until CTEP has sent an amendment 'approval-letter' to the study Principal Investigator or Chair. If required the CIRB will include a summary of changes that have been made since CTEP review. CTEP will assess if any changes have been made and if additional CTEP review is required. CTEP will notify the study Principal Investigator or Chair regarding the final outcome of the amendment (i.e. approval or disapproval).